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THE EFFECT OF OPERATIONS ON THE EXCRETION OF TOTAL 17-HYDROXYCORTICOSTEROIDS IN ELDERLY PATIENTS

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I. INTRODUCTION

The aging has in the last decades attained an increased interest and significance. Following the gradual rise in the population in the older age groups, the number of surgical operations involving subjects of old age has also increased and presents an urgent medical problem. Modern methods of anaesthesia and chemotherapy have greatly improved the possibility of subjecting old persons to surgical measures and many patients who previously have been considered poor risks are now operated upon. It is therefore important to assess the fitness of old patient for operation. The ability of patients to endure operations is influenced in a large degree by the secretion of glucocorticoids, especially of hydrocortisone, released by the adrenal cortex. Animal experiments and clinical observations of normal and abnormal function of the adrenal cortex have revealed that a normal activity of this gland is essential to ensure that a patient can withstand the stress of operation. It would therefore be of advantage to evaluate the suitability of the patient for operation by examining the activity of the adrenocortical secretion preoperatively or in connection with operations, by determining the content of 17-hydroxysorticosteroids in the blood (42, 37) or their excretion in urine (26). It is well known that the excretion of steroids, at least that of 17-ketosteroids and estrogens, diminishes with age in old persons (6, 8, 16, 17, 25, 27). Also the content of dehydroepiandrosterone has been observed to diminish with age (41). However, the level of 17-hydroxycorticosteroids in the plasma has been nearly the same in the older as in the younger age groups (41). It would therefore be of important to study the increase of the excretion of total 17-hydroxycorticosteroids in old persons due to surgical measures. The amount of this excretion reflect to some extent the degree of stress resulting from the operation.

The aging is related to endocrine function (3, 7, 8). For instance, the function of ovaries and testes diminishes almost completely with age. Androgenic and estrogenic hormones have normally an anabolic effect on the organism. They promote the tissue proliferation and the phenomenon of growth. Deficiency of these hormones may disturb the balance of the endocrine system. In advancing age the deficiency of sex hormones may favour the effect of the glucocorticoid system of the adrenal cortex on the organism to stress conditions, and may increase the protein catabolism. The organism life is under a continuous change. The amount of connective tissue increases in ratio to parenchymal tissue and the period of recovery from exhaustion increases. All these changes are most clear in connective tissue where the number of capillaries is small and the transport and diffusion of nutritional agents decrease. The water content of tissues diminishes and the colloidal substances may concentrate. The contents of protein substances and tissue nitrogen increase. A typical dehydration of body cells is followed by a deposition of calcium and cholesterol as a result of changes in the tissue colloids. The reaction of certain connective tissues, e.g. in capillaries, to mechanical or chemical stimuli is weaker and slower than in younger persons. The reaction of the organism is continuously changing and the aging includes metabolic involutions which are not caused by diseases.

It is generally recognized that an operation imposes a great stress on an aged patient. Since his blood circulation may be impaired, anoxia may result, and the tissue reactions may be deficient. Planned surgical measures in old patients frequently necessitate more care in preoperative and postoperative treatment. The symptoms of acute surgical diseases in old patients may differ radically from those observed in younger subjects (33). Degenerative changes in vital organs are common in the former and may lead to postoperative complications. Greater attention must be paid in the preoperative period to the treatment of the heart, kidneys and lungs. In recent years preoperative breathing exercises have been introduced as an aid in preparing patients for surgery. Older people generally cannot tolerate large intravenous liquid infusions in the postoperative stage and subcutaneous liquid infusions tend to delay the mobilization of the

patient. Old persons react less sensitively to pain and also their reactions to acute inflammatory diseases are weak. These observations apply also in the postoperative stage. The clinical symptoms of stress are consequently much weaker in such persons.

It is well known that the organism increases the secretion of adrenal corticosteroids through the mediation of the pituitary adrenocorticotrophic hormone in stress conditions (45, 30, 43, 39, 52, 53). Thus, for instance, an operation leads to an increase in the content of adrenal corticosteroids in the blood (42, 51, 9, 16) or an increase in the excretion of total 17-hydroxycorticosteroids in the urine (48,18,15). In earlier studies (53) the content of 17-hydroxycorticosteroids in the blood has been observed to increase clearly during the first few hours in connection with biliary and intrathoracic operations, and remains high after the latter up to the third postoperative day. The amount of total 17-hydroxycorticosteroids in the urine may be considered an indicator of the activity of the adrenal cortex in cases of major surgery (15). In earlier studies a high excretion of total 17-hydroxycorticosteroids in the urine has been observed in connection with pulmonary and abdominal operations by Halme, Pekkarinen and Turunen (15). Increased amounts of reducing corticoids after enzymatic hydrolysis and 17-ketosteroids have been observed after surgery (2). Increases in the amounts of free 11-oxycorticosteroids in the urine have also been established in wounded and operated patients (22, 19, 4). This excretion of free 11-oxycorticosteroids in the urine does not increase as clearly as the excretion of total 17-hydroxycorticosteroids (5, 32).

In previous studies it has been established that the eosinophil cells may almost completely disappear from the blood as a result of increased excretion of adrenocortical steroids and adrenaline during the first two days following lung operations (31, 36). The reaction of eosinophil cells has often been nearly maximal after thoracic operations due to a high sensitivity of the reaction of eosinophil cells to adrenocortical hormones. In an earlier study, Uotila and Pekkarinen (52) have observed that the activity of the suprarenal cortex may increase greatly in cases of surgical shock. The weight of the adrenal glands increased on the average 75 per cent, while at the same time the contents of adrenalin, cholesterol and vitamin C decreased, in some cases clearly.

It can be assumed that in old patients and in persons who have suffered from chronic diseases the functions of the suprarenal cortex may in some cases be inadequate. The excretion of 17-ketosteroids is known to be clearly weaker in old persons (16, 17, 24, 27, 6). In connection with major operations on patients suffering from severe chronic diseases, substitution therapy with adrenocortical hormones may be appropriate if the function of the suprarenal cortex is inadequate, or the stimulation produced by ACTH released by the pituitary is weak (4). Administration of adrenocorticotrophic hormone or cortisone has in certain cases yielded favourable results after surgical operations (12, 50, 23, 38). In some cases in which treatment of shock has been ineffective, intravenous administration of cortisone has proved beneficial (20, 21, 47). Sometimes hydrocortisone and ACTH are able to reinstate normal blood circulation and increase the blood pressure, and at same time improve the general condition of the patient.

II. THE PURPOSE OF THE INVESTIGATION

The purpose of the investigation has been to study the response of the adrenal-pituitary system in aged persons in connection of various operations by determining the excretion of total 17-hydroxycorticosteroids in the urine.

III. MATERIAL AND METHOD

The material included 52 patients of whom 51 had been subjected to surgical operations. Twenty-two patients were men, 30 women. The mean age was 63.5 years (men 62 years and women 64.5 years). Fifteen of the patients were over 70 years old. The operations included 12 thoracic operations, 26 abdominal operations, 7 urological operations and 6 nailings of femoral necks.

The total 17-hydroxycorticosteroids were analysed in 332 24-hour urine samples, 62 taken before and 280 after operation; 130 were from the men and 150 from the women. The total 17-hydroxycorticosteroid excretion was followed 1-3 days before and 1-7 days after the operation. The 24-hour urine samples were acidified with sulphuric acid to pH 2-3 in order to permit the determination of the noradrenaline and adrenaline contents.*) The total 17-hydroxycorticosteroid determinations were performed using the method of *Jenkins* et al. (26) in which the total 17-hydroxycorticosteroids in the samples are extracted with butanol. The butanol employed was purified before use by treating it several days with a phenylhydrazine-sulphuric acid solution to remove chromogenic substances and then distilling twice at 117° C. The resulting butanol was free of chromogens. The urine was diluted twice before the determination since the phenylhydrazine-sulphuric acid colour is sometimes inhibited in undiluted urine. Hydrocortisone alcohol (200 μg/ml) (Ciba, Schering, Organon) was added as a standard to parallel samples in each series. The standard deviation of replicate determinations was found by computing $\frac{3.8.}{\sqrt{n}}$

*) To be published later.

IV. RESULTS

1. WHOLE SERIES (Table 1, Fig. 1)

a. BEFORE THE OPERATION

Sixty two 24-hour urine samples from one to three days before the operation from 31 patients (13 men and 18 women) were analysed.

The mean daily excretion of total 17-hydroxycorticosteroids in the urine was 5.7 mg (men 6.5 mg and women 5.2 mg). The basal excretion was over 10 mg in 24 hrs in 4 patients, and in two of these over 20 mg in 24 hrs. In eight patients the daily excretion was 1.0 mg in 24 hrs or less.

b. DURING AND AFTER OPERATION

Twohundred and eighty 24-hour urine samples from 1 to 7 days after the operations from 52 patients (22 men and 30 women) were analysed.

The mean excretion of total 17-hydroxycorticosteroids during the first day after operation was 16.0 mg, during the second 21.7 mg and during the third 15.7 mg. The exretion during the second day after operation was nearly four times the mean excretion before the operation. The excretion during the third day was still three times the excretion before operation. The mean excretion in the urine during the first three days after the operation was found to exceed the mean excretion before the operation in most of the patients. The mean excretion on the fourth day was nearly twice the preoperative value, but on the fifth day the excretion diminished to the level before operation. — The total excretion of 17-hydroxycorticosteroids thus reaches its highest level on the first and second days after

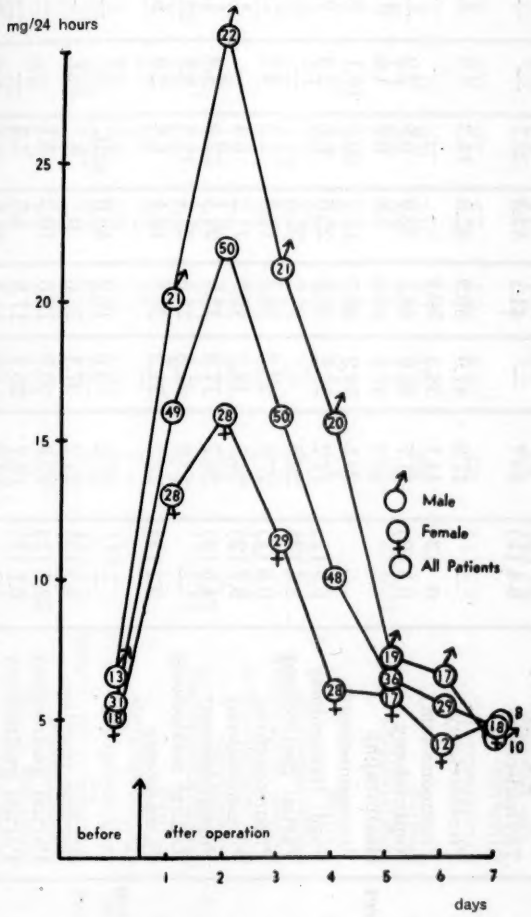

Fig. 1. — Excretion of total 17-hydroxycorticosteroids in the urine of 52 elderly patients 22 men and 30 women). The numbers of patients are indicated inside of circles.

the operation. The maximum excretion occurred in both sexes on the second day after the operation. The excretion is almost normal after the fifth day. The reaction of the men to the operations lasted about four days and that of the women about three days.

TABLE 1

EXCRETION (MG IN 24 HOURS) OF TOTAL 17-HYDROXYCORTICOSTEROIDS IN THE URINE BEFORE AND AFTER OPERATION

No. of Cases	Age Years	Sex	Diagnosis	Operation	Mean Excretion		Excretion after Operation						
					Before Operation	1—3 Days after Operation	1st Day	2nd Day	3rd Day	4th Day	5th Day	6th Day	7th Day
1	78	Male	Hypertrophy of the prostate	Laparotomy	5.1 (1)	67.5	10.0	19.1	173.5	179.2	26.6	—	—
2	53	„	Duodenal ulcer	Gastrojejunostomy	—	54.0	44.8	77.4	39.7	12.1	22.5	20.5	13.3
3	61	Female	Nodular goitre	Thyroidectomy	6.4 (1)	48.7	—	44.1	53.3	33.1	—	—	—
4	79	Male	Hypertrophy of the prostate	Prostatectomy	—	47.9	41.9	59.9	42.0	14.3	5.8	5.4	6.9
5	51	„	Bronchial carcinoma	Pneumonectomy	0 (3)	44.1	38.3	50.0	—	—	—	—	—
6	52	Female	Renal tuberculosis	Nephrectomy	0.3 (2)	41.7	42.0	44.1	38.9	0.9	2.2	—	—
7	54	Male	Perforated gastric ulcer	Gastroraphy	—	40.7	57.6	59.0	5.6	0.2	1.0	0	1.6
8	65	„	Bronchial carcinoma	Pneumonectomy	—	39.5	59.2	42.0	17.2	20.3	19.1	9.4	—
9	62	„	Bronchial carcinoma	Expl. thoracotomy	6.5 (1)	31.2	23.2	46.8	23.5	6.6	2.6	9.0	0.8
10	58	„	Gastric ulcer	Partial gastrectomy	2.4 (3)	29.8	—	38.2	21.5	—	—	—	—
11	60	„	Bronchial carcinoma	Pneumonectomy	0.8 (1)	27.0	28.3	38.4	14.3	5.3	3.2	7.6	2.5
12	58	„	Bronchial carcinoma	Pneumonectomy	9.7 (2)	24.8	14.2	49.0	11.2	6.4	—	1.3	0
13	56	„	Bronchial carcinoma	Pneumonectomy	24.6 (3)	24.7	17.6	35.0	21.4	12.0	4.4	1.8	2.4
14	54	Female	Mammary cancer	Radical mastectomy	—	23.9	21.8	28.6	21.4	12.3	9.9	12.6	—
15	60	Male	Intrathoracic goitre	Thoracotomy	3.2 (3)	22.2	21.3	25.8	19.4	8.5	2.9	5.8	6.1
16	53	Female	Skull fracture, laceration of the lung, shock	—	—	21.5	8.0	10.2	46.0	exit.	—	—	—
17	55	„	Cardiac cancer	Cardiac resection	4.3 (3)	21.2	37.1	26.6	0	0	exit.	—	—
18	61	„	Gastric ulcer	Partial gastrectomy	32.1 (1)	17.9	28.9	14.5	10.2	3.1	—	—	—
19	52	„	Gastric ulcer	Partial gastrectomy	6.1 (1)	16.7	25.7	17.8	6.5	7.4	—	—	—
20	60	„	Obstruction by adhesions	Liberation	1.3 (3)	16.7	18.0	20.3	11.9	4.8	8.2	2.6	—
21	56	Male	Perforated gastric ulcer	Gastroraphy	—	16.5	22.0	13.4	14.1	12.3	9.9	12.6	—
22	60	Female	Gastric cancer	Partial gastrectomy	2.7 (1)	16.2	19.0	23.5	6.0	4.0	2.8	0.5	3.5
23	55	Male	Bronchial carcinoma	Pneumonectomy	—	12.8	0	23.8	14.6	11.4	10.2	5.9	—
24	60	Female	Cholelithiasis	Cholecystectomy	—	12.5	11.8	10.1	15.7	7.9	—	—	—
25	78	„	Fract. of the fem. neck	Nailing	7.5 (1)	12.5	9.5	16.7	11.3	6.2	—	—	—
26	72	„	Fract. of the fem. neck	Nailing	—	12.5	14.3	—	10.6	2.2	0	0	—
27	61	„	Gastric cancer	Partial gastrectomy	5.5 (2)	12.2	14.0	10.4	12.1	9.8	3.4	5.8	5.8

24	60	Female	Cholelithiasis	Cholecystectomy	—	12.5	11.8	10.1	15.7	7.9	—	—	—	
25	78	„	Fract. of the fem. neck	Nailing	7.5 (1)	12.5	9.5	16.7	11.3	6.2	—	—	—	
26	72	„	Fract. of the fem. neck	Nailing	—	12.5	14.3	—	10.6	2.2	0	0	—	
27	61	„	Gastric cancer	Partial gastrectomy	5.5 (2)	12.2	14.0	10.4	12.1	9.8	3.4	5.8	5.8	
28	45	„	Cholelithiasis	Cholecystectomy	0 (2)	12.2	20.6	10.3	5.0	3.8	3.8	3.8	2.7	
29	63	„	Cholelithiasis	Cholecystectomy	9.1 (3)	12.0	8.4	20.9	6.8	6.0	3.3	5.2	6.6	
30	57	Male	Bronchial carcinoma	Pneumonectomy	0.6 (3)	11.9	18.8	10.8	6.0	2.1	1.8	1.2	—	
31	67	Female	Gastric neurinoma	Partial gastrectomy	0 (2)	11.4	4.6	21.4	8.3	0	—	—	—	
32	74	„	Carcinosis	Laparotomy	—	10.0	3.8	17.4	8.9	1.5	—	—	—	
33	71	„	Costal caries	Resection of ribs	9.9 (3)	9.2	10.7	12.5	4.4	9.3	9.8	—	—	
34	64	„	Cholecystitis	Cholecystectomy	—	9.0	7.0	10.4	9.6	3.6	—	—	—	
35	61	„	Carcinoma of the rectum	Excision of the rectum	1.1 (1)	8.8	9.2	11.0	6.3	18.6	21.6	10.4	6.3	
36	64	„	Carcinoma of the rectum	Left colostomy	1.2 (1)	8.8	10.3	9.9	6.2	8.8	6.2	2.8	5.5	
37	71	„	Cholecystitis	Cholecystectomy	—	7.8	—	8.6	7.0	3.5	2.8	—	—	
38	82	„	Fract. of the fem. neck	Nailing	—	7.3	7.4	8.9	5.5	4.6	4.5	—	—	
39	52	Male	Gastric cancer	Gastrojejunostomy	14.3 (1)	7.2	4.1	13.4	4.1	1.2	15.7	4.9	6.4	
40	69	„	Periduodenitis	Laparotomy	—	6.8	2.2	12.8	5.4	0	0	—	—	
41	59	Female	Pyloric stenosis	Gastrojejunostomy	4.2 (2)	6.4	4.1	10.9	4.1	1.3	—	—	—	
42	62	Male	Gastric cancer	Partial gastrectomy	—	6.3	0.8	16.4	1.8	11.1	3.8	16.9	—	
43	63	Female	Cholelithiasis	Cholecystectomy	1.0 (2)	5.8	6.2	5.2	6.0	2.6	1.7	7.1	5.2	
44	80	„	Fract. of the fem. neck	Nailing	—	4.9	7.8	5.2	1.8	2.1	—	—	—	
45	56	Male	Hypertrophy of the prostate	Prostatectomy	12.9 (2)	4.7	6.2	3.2	4.6	0.8	1.1	0	—	
46	74	Female	Fract. of the fem. neck	Nailing	—	4.4	0.2	7.9	5.1	6.6	0	0	2.6	
47	73	Male	Hypertrophy of the prostate	Prostatectomy	0.3 (1)	4.1	9.8	0.7	1.9	3.6	0.5	4.0	5.4	
48	76	„	Hypertrophy of the prostate	Dilatation of the prostate	4.1 (4)	3.5	2.5	2.7	5.3	3.6	2.5	3.8	—	
49	79	Female	Fract. of the fem. neck	Nailing	—	3.2	4.4	2.4	2.8	7.5	14.4	—	—	
50	73	„	Renal cyst	Excision	0.7 (3)	3.2	5.6	0.9		—	—	—	—	
51	70	Male	Prostatic cancer	Castration	—	2.4	1.3	6.0	0	1.8	0	—	—	
52	66	Female	Carcinoma of the gall-bladder	Laparotomy	—	1.3	0.9	—	1.6	0.6	4.1	0	—	
Mean	63.5				5.7		16.0	21.7	15.7	10.1	6.5	5.5	4.7	
	62	Males	(22 cases)		6.5		20.2	29.3	21.3	15.6	7.0	6.5	4.5	
	64.5	Females	(30 cases)		5.2		12.9	15.8	11.5	6.1	5.8	4.2	4.8	

2. MEN AND WOMEN

a. ALL OLD PATIENTS (Fig. 1)

When the excretion of total 17-hydroxycorticosteroids in the urine of the men and women was followed from one to seven days after the operations, the mean excretion was higher for the men than for the women on the first and second day after the operations. The mean excretion of total 17-hydroxycorticosteroids during the first 2 days after operation seems to be clearly higher in the male than in the female group. It should be remembered, that the patients were subjected to different types of operations, and hence the male and female groups cannot be directly compared.

The mean excretion of total 17-hydroxycorticosteroids in the urine of 22 *men* on the first day following the operation was 20.2 mg, on the second day 29.3 mg and on the third day 21.3 mg. On the second day after operation the mean excretion for the men was nearly five times, and on the first and third days nearly three times the preoperative excretion.

The excretion of total 17-hydroxycorticosteroids in the urine by 30 *women* was 12.9 mg on the first day, 15.8 mg on the second day and 11.5 mg on the third day after the operation; and thus respectively, more than twofold, about threefold, and more than twofold the excretion before operation. These excretions of total 17-hydroxycorticosteroids in women are half as great as the corresponding excretions for the men. In both sex groups the excretions become normal during the fourth to seventh days. The excretion of total 17-hydroxycorticosteroids during the fourth day after operation was still higher for the men (15.6 mg) than for the women (6.1 mg), but the excretion on the fifth day were almost equal for men (7.0 mg) and women (5.8 mg).

b. VARIOUS OPERATION GROUPS (Table 2, Fig. 2)

Since the patients had been operated upon for various types of lesions, it was considered appropriate to examine the excretion of total 17-hydroxycorticosteroids by men and women in two operation groups, in the group of abdominal operations and in the subgroup of gastric operations.

Abdominal operations (Fig. 2)

In the group of eight *men* on whom abdominal operations were performed, the mean excretion of total 17-hydroxycorticosteroids was 7.3 mg prior to the operation, 20.2 mg on the first day, 31.2 mg on the second day, 33.3 mg on the third day, and 30.9 mg on the fourth day following the operations. One patient of this group had a very high excretion of total 17-hydroxycorticosteroids on the third and fourth day which increased the mean excretion for the whole group on these days. — The mean excretion of total 17-hydroxycorticosteroids in the urine of 18 *women* was relatively low, only 3.0 mg in 24 hrs, before the operation. An increased excretion in the urine was observed after the operation, but the increase in women was considerably smaller than in the men. During the first three days after the operations the mean excretions in women were 12.8 mg, 14.7 mg, and 7.3 mg in 24 hrs. The excretion on the third day after operation is lower, but still higher than the preoperative excretion. The excretion on the fourth day was on the normal level. When compared with the mean excretion before operation, the amounts of total 17-hydroxycorticosteroids on the first and second days are respectively four and five times as great. Furthermore, the mean excretions for the men for the first two days after operation are twice as high as the corresponding mean exretions in women.

It is thus seen that the total 17-hydroxycorticosteroid excretion in the men in connection with abdominal operations is high during the first two postoperative days, although the high value for one patient increased also the values for the third and fourth days. Even during the fifth to seventh days after operation the mean excretion was clearly higher for the men than for the women.

Gastric operations (Table 2)

The group on whom gastric operations were performed can be considered fairly uniform. It comprised 6 men (mean age 56 years) and 7 women (mean age 59.5 years). The mean excretion of total 17-hydroxycorticosteroids in the group of gastric operations was for the *men* 8.4 mg in 24 hrs prior to the operations and rose

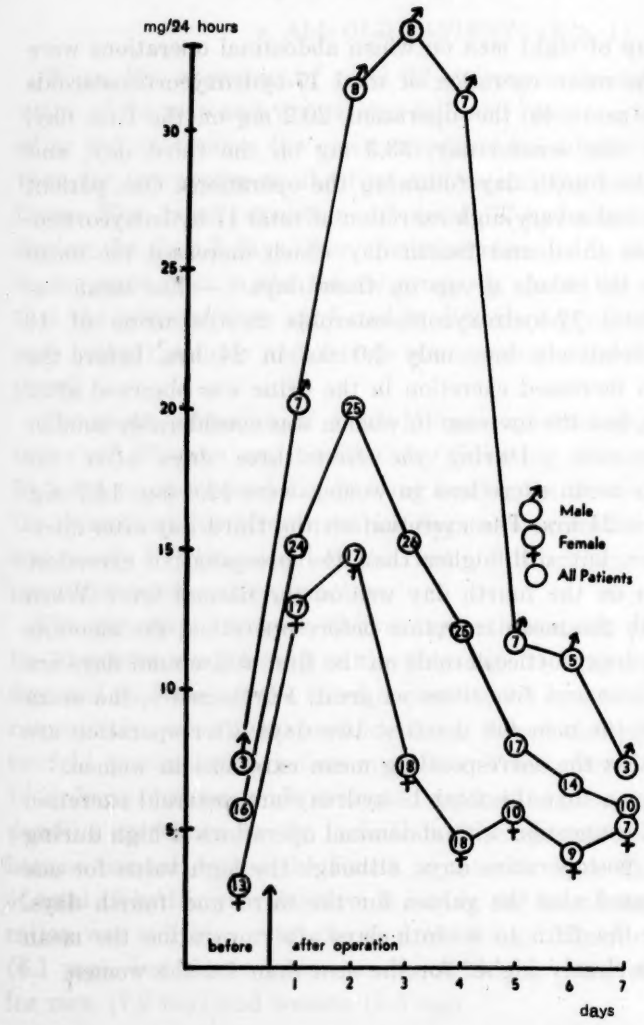

Fig. 2. — Excretion of total 17-hydroxycorticosteroids in the urine. Abdominal operations (26 cases; 8 men and 18 women). The numbers of patients are indicated inside of circles.

to 25.9 mg on the first day after operation and to 36.3 mg on the second, but diminished to 14.3 mg on the third day. The increase in the excretion of total 17-hydroxycorticosteroids was thus very

TABLE 2

EXCRETION OF TOTAL 17-HYDROXYCORTICOSTEROIDS IN THE URINE (MG IN 24 HOURS). GASTRIC OPERATIONS IN MEN AND WOMEN.

No. of Cases	Surgical Measures	Sex	Mean Age Years	Before	After Operation						
					1st Day	2nd Day	3rd Day	4th Day	5th Day	6th Day	7th Day
6	2 partial gastrectomies ..... 2 gastrojejunostomies ..... 2 gastroraphies ..	Male	56	8.4	25.9	36.3	14.3	7.4	10.6	11.0	7.1
7	5 partial gastrectomies ..... 1 cardiac resection 1 gastrojejunostomy	Female	59.5	7.8	19.1	17.9	6.7	3.7	3.1	3.2	4.7

great among the men, especially during the first two days after operation. After the fourth day, the mean excretion was close to the level before the operation.

For the *women* of the group of gastric operations the mean excretion of total 17-hydroxycorticosteroids was 7.8 mg before the operations and rose to 19.1 mg on the first, to 17.9 mg on the second, but decreased to 6.7 mg on the third day following the operations. The increase in the excretion was fairly great, but not as pronounced as for the men. In particular the mean excretion of total 17-hydroxycorticosteroids during the second postoperative day was nearly twice as high in the men as in the women. On the fourth day after the operations, the mean excretion in the group of women was slightly below the preoperative level, but within the normal range.

TABLE 3

EXCRETION OF TOTAL 17-HYDROXYCORTICOSTEROIDS IN THE URINE (MG IN 24 HOURS). TWO AGE GROUPS OF ELDERLY PATIENTS.

No. of Cases	Surgical Measures	Sex	Mean Age Years	Before	After Operation						
					1st Day	2nd Day	3rd Day	4th Day	5th Day	6th Day	7th Day
7	1 pneumonectomy	Male	73	3.3	18.1	20.2	35.0	33.3	7.8	5.7	6.2
	2 prostatectomies										
	2 laparotomies										
	1 prostate dilatation ..										
	1 castration										
15	6 pneumonectomies	„	56.5	7.5	21.1	33.4	14.4	6.9	6.6	6.8	4.1
	2 thoracotomies										
	2 partial gastrectomies										
	2 gastrojejunostomies ..										
	1 prostatectomy										
	2 gastroraphies										
16	6 nailings of the femoral neck	Female	71.5	4.2	6.7	10.6	6.4	4.3	4.7	2.5	5.0
	1 partial gastrectomy ..										
	4 cholecystectomies										
	2 expl. laparotomies ..										
	1 excision of renal cyst .										
	1 resection of ribs for periosteal tuberculosis										
	1 left colostomy										
14	4 partial gastrectomies	„	56.5	5.6	20.0	20.4	16.9	8.2	7.4	6.0	4.4
	1 cardiac resection										
	1 thyroidectomy										
	1 radical mastectomy ...										
	1 nephrectomy										
	2 cholecystectomies										
	1 excision of rectum ...										
	1 gastrojejunostomy ...										
	1 laparotomy										
	1 shock therapy										

3. EFFECT OF AGE (Table 3 and 4)

In order to assess the influence of age the patients were divided into two groups, those above and those below the mean age of the whole series, 63 years.

TABLE 4

EXCRETION OF TOTAL 17-HYDROXYCORTICOSTEROIDS IN THE URINE (MG IN 24 HOURS). ABDOMINAL OPERATIONS IN WOMEN OF TWO AGE GROUPS.

No. of Cases	Surgical Measures	Mean Age Years	Before	After Operation						
				1st Day	2nd Day	3th Day	4th Day	5th Day	6th Day	7th Day
8	4 cholecystectomies 1 partial gastrectomy ..... 2 expl. laparotomies 1 left colostomy ..	66.5	2.8	5.9	13.4	6.8	3.3	3.6	3.8	5.8
10	4 partial gastrectomies ..... 1 cardiac resection 2 cholecystectomies 1 excision of rectum 1 gastrojejunostomy ..... 1 laparotomy	57.5	5.7	18.9	15.6	7.8	6.1	8.0	4.6	4.6

a. MEN

OLDER AGE GROUP

Mean age 73 years

The group of *older* men comprised 7 patients. Before the operations the mean excretion of total 17-hydroxycorticosteroids was 3.3 mg/24 hrs. The excretion during the first day after operation was 18.1 mg and during the second 20.2 mg/24 hrs. The high excretion for the group on the third and fourth days after operation is due to the very high values recorded for one member of the group (No. 1).

YOUNGER AGE GROUP

Mean age 56.5 years

In the *younger* age group there were 15 patients. This group included a number of patients on whom pneumonectomy was performed and who had high postoperative excretions. The mean daily excretion of total 17-hydroxycorticosteroids in the urine was 7.5 mg preoperatively and rose to 21.1 mg on the first day after the operations and to 33.4 mg on the second day. On the third day it was still 14.4 mg, but practically normal subsequently. — The excretion on the second day is seen to be

much higher in the younger than in the older age group, but this is evidently partly due to the occurrence of six subjects in the former group on whom pneumonectomies were performed which due to the severity of the operations resulted in a high excretion of total 17- hydroxycorticosteroids.

b. WOMEN

OLDER AGE GROUP

Mean age 71.5 years

The group of *older women* comprised 16 patients. Their mean excretion of total 17-hydroxycorticosteroids before the operations was 4.2 mg in 24 hrs. The mean excretion increased relatively slowly being 6.7 mg on the first day and 10.6 mg in 24 hrs on the second. The group included six patients who were operated upon for fracture of the femoral neck, which operation had only a slight influence on the steroid excretion. The mean excretion of total 17-hydroxycorticosteroids was only slightly above normal on the third day and subsequently within the normal range.

YOUNGER AGE GROUP

Mean age 56.5 years

In the group of *younger women* there were 14 patients. The mean excretion of total 17-hydroxycorticosteroids in the urine was 5.6 mg before the operations, 20.0 mg on the first, 20.4 mg on the second, and 16.9 mg on the third day after operation. The mean excretion of total 17-hydroxycorticosteroids underwent a clear decrease on the fourth day and fell to the normal level during the fifth to seventh days. The operations in this younger group of women were fairly large ones, but the mean excretions are not so high as in the corresponding age group of men.

Influence of age was studied also in the group of 18 *abdominal operations* in women. The mean ages were 66.5 and 57.5 years. The excretion of total 17-hydroxycorticosteroids was before operation 2.8 mg in the older group and 5.7 mg in the younger.

During the first three days after operation the excretion was in the older age group 5.9 mg, 13.4 mg, 6.8 mg, and in the younger age group 18.9 mg, 15.6 mg, and 7.8 mg respectively. In older age group the mean excretion is smaller than in the younger group.

On the first day after operation the excretion in younger age group has been three times the excretion in the older group. This is also partly due to the smaller excretion of urine in older age group than in younger age group.

4. VARIOUS OPERATION GROUPS

The mean excretion of total 17-hydroxycorticosteroids was also determined for the patients in different operation groups: thoracic operations (12 cases), abdominal operations (26 cases), urological operations (7 cases) and nailings of femoral necks (6 cases).

a. THORACIC OPERATIONS (Fig. 3)

On the 12 patients thoracic operations were performed (8 men had pulmonary carcinoma, one man and one woman goitre, one woman mammary carcinoma, one woman costal caries, and one woman trauma of the thorax associated with shock). The shock patient will be discussed in the group of individual cases. The mean age of the group was 59 years.

The mean excretion of total 17-hydroxycorticosteroids in the urine of the twelve patients was 6.9 mg in 24 hrs preoperatively. It increased clearly after the operations, being 23.0 mg, 33.9 mg and 18.8 mg on the first three postoperative days. The very high excretion of total 17-hydroxycorticosteroids on the second day is noteworthy; it is nearly five times the preoperative excretion. The mean excretion after operation fell to the preoperative level by the fifth day, 7.1 mg, and decreased further to 6.1 mg on the sixth and 2.4 mg on the seventh day.

Intrathoracic operations (Table 5)

The patients, all men, on whom intrathoracic operations were performed, will be discussed as a separate group (9 patients). The group included seven patients with pulmonary carcinoma who were subjected to pneumonectomy, one patient who was subjected to explorative thoracotomy, and one patient with intrathoracic goitre. The mean age of the patients was 59 years.

The mean excretion of total 17-hydroxycorticosteroids in the urine before operation was 6.5 mg. The mean daily excretions of total 17-hydroxycorticosteroids for the first four postoperative days were 24.6 mg, 36.8 mg, 15.9 mg and 9.1 mg. The excretion of total 17-hydroxycorticosteroids on the second day is the highest for all our groups, and is six times the preoperative excretion for

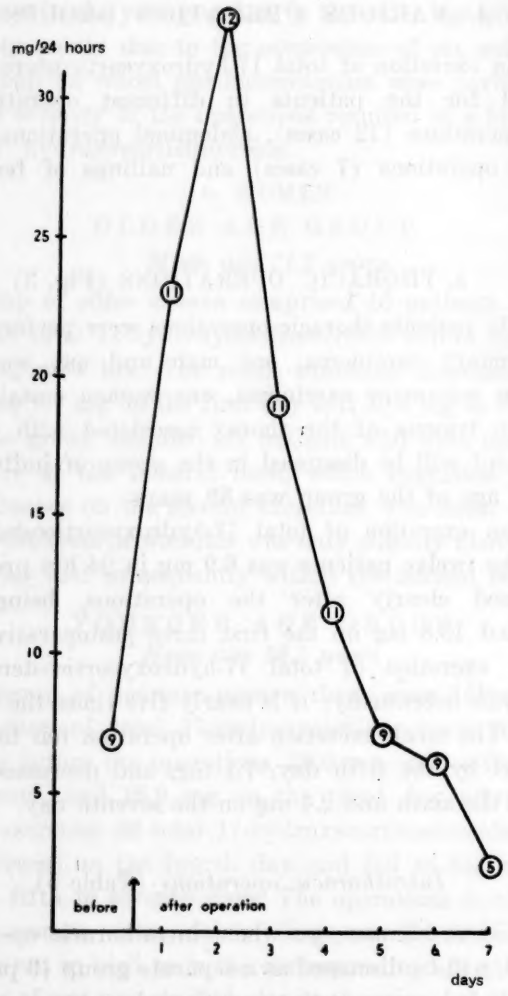

Fig. 3. — Excretion of total 17-hydroxycorticosteroids in the urine before and after thoracic operations (12 cases). The numbers of patients are indicated inside of circles.

this group. The mean excretion reverted to normal before the operations by the fifth day. The greatest increase in steroid excretion was observed among the patients with pulmonary carcinoma who were subjected to pneumonectomy.

TABLE 5

EXCRETION OF TOTAL 17-HYDROXYCORTICOSTEROIDS IN THE URINE (MG IN 24 HOURS) IN PATIENTS OF CERTAIN OPERATION GROUPS.

No. of Cases	Surgical Measures	Mean Age Years	Before	After Operation						
				1st Day	2nd Day	3rd Day	4th Day	5th Day	6th Day	7th Day
9	*Intrathoracic Operations* .... 7 pneumonectomies 1 expl. thoracotomy ..... 1 thoracotomy ...	58	6.5	24.6	36.8	15 9	9.1	6.3	5.3	2.4
13	*Gastric Operations* 7 partial gastrectomies ..... 3 gastrojejunostomies ..... 1 cardiac resection 2 gastroraphies ..	57.5	8.0	21.9	26.4	10.3	5.2	8.3	8.7	6.7
6	*Cholecystectomies*	61	3.4	8.8	10.9	8.4	4.6	2.9	5.4	4.8
3	*Prostatectomies* ..	69	6.1	19.3	21.3	16.2	6.2	2.5	3.1	6.2

b. ABDOMINAL OPERATIONS (Fig. 2)

Abdominal operations were performed on 26 patients (8 men and 18 women). 7 cases of gastric ulcer, 1 case with duodenal ulcer, 5 cases with gastric cancer, 2 cases with rectal carcinoma, one case with abdominal carcinosis, 6 cases with cholecystopathy, 1 case of carcinoma of the gall-bladder, 1 case with duodenitis, 1 case with intra-abdominal adhesions and 1 case with hypertrophy of the prostate. Their mean age was 61.5 years (men 60 and women 62 years).

The excretion of total 17-hydroxycorticosteroids in the urine in the group of abdominal operations before the operations was 5.6 mg in 24 hrs. The daily excretions on the first three days after operations were 15.0 mg, 20.0 mg, and 15.3 mg. Abdominal operations increase the excretion of total 17-hydroxycorticosteroids in the urine during the first three postoperative days. The maximum excretion occurred during the second day. The excretion

was higher also on the fourth day (12.1 mg) than before the operations. It returned to normal during the fifth to seventh days.

Gastric operations (Table 5)

The gastric operations comprised partial gastrectomies, gastrojejunostomies and gastroraphies. The mean age of the 13 patients (6 men and 7 women) was 57.5 years. The preoperative excretion of total 17-hydroxycorticosteroids in this group was 8.0 mg in 24 hrs. The excretions on the first three postoperative days were 21.9 mg, 26.4 mg and 10.3 mg. The excretion of total 17-hydroxycorticosteroids was thus high on the first two days after the operations, but diminished on the third day, but was still slightly higher than the mean preoperative value for the group.

Cholecystectomies (Table 5)

The second group of abdominal operations involved operations on the gall-bladder. The six patients were all women (mean age 61 years).

The daily excretion of total 17-hydroxycorticosteroids in the urine was preoperatively 3.4 mg, on the first postoperative day 8.8 mg, on the second 10.9 mg and on the third 8.4 mg. The increased excretion of total 17-hydroxycorticosteroids continued the first three days postoperatively but then returned to the normal level after the fourth day. The increase of total 17-hydroxycorticosteroids in the urine was lower than in the other abdominal operation groups.

c. UROLOGICAL OPERATIONS (Fig. 4)

The third group of operations comprised urological operations. The mean age of the 7 urological patients (5 men, 2 women) was fairly high, 68.5 years. The patients included 4 cases of hypertrophy of the prostate, one case of prostatic cancer, 1 case of renal tuberculosis, and 1 case of renal cyst. The last two patients were women.

The mean daily excretion of total 17-hydroxycorticosteroids was 3.7 mg before the operations. On the first three postoperative days the excretion of total 17-hydroxycorticosteroids was 15.6, 16.8, and 15.5 mg in 24 hrs, but returned to the normal level on the fourth day.

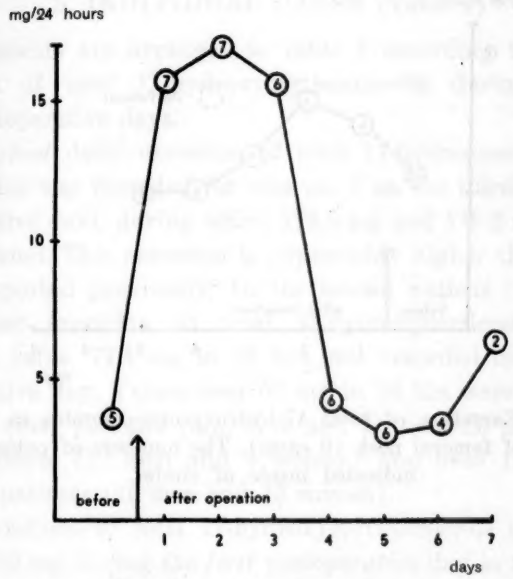

Fig. 4.— Excretion of total 17-hydroxycorticosteroids in the urine. Urological operations (7 cases). The numbers of patients are indicated inside of circles.

Prostatectomies (Table 5)

The excretion of total 17-hydroxycorticosteroids in the urine was followed in three patients on whom prostatectomies were performed. The mean age was 69 years. The mean daily excretion of total 17-hydroxycorticosteroids rose from 6.1 mg before the operation to 19.3 mg on the first postoperative day and to 21.3 mg on the second, but diminished to 16.2 mg on the third day. The mean excretion was within the normal range from the fourth day.

d. NAILING OF FEMORAL NECK (Fig. 5)

Six patients had fractures of the femoral neck, and were subjected to surgery under local anaesthesia. The mean age of these patients, all women, was 77.5 years. The excretion of total 17-hydroxycorticosteroids increased only slightly during the first

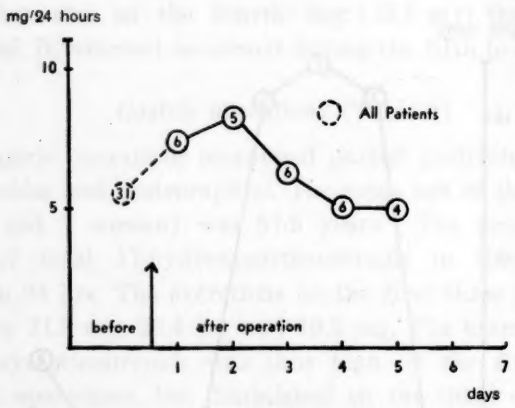

Fig. 5. — Excretion of total 17-hydroxycorticosteroids in the urine. Nailings of femoral neck (6 cases). The numbers of patients are indicated inside of circles.

two days (7.3 mg and 8.2 mg) after the operations and returned to normal during the fourth postoperative day. The increase in the excretion of total 17-hydroxycorticosteroids was smaller than in other groups.

e. COMPARISON OF THE EXCRETION IN THE DIFFERENT OPERATION GROUPS

Since a maximum excretion of total 17-hydroxycorticosteroids in the urine was found in all groups on the second postoperative day, it is interesting to compare the amounts of the highest excretions. The maximum excretion of total 17-hydroxycorticosteroids, 33.9 mg in 24 hrs for the group of thoracic operations, was followed by the group of abdominal operations with 20.0 mg in 24 hrs, the group of urological operations with 16.8 mg in 24 hrs, and the group of femoral neck nailings with only 8.2 mg in 24 hrs. The similar order is observed also on the first and third postoperative days.

5. INDIVIDUAL CASES (Table 1)

The patients are arranged in table 1 according to the mean excretions of total 17-hydroxycorticosteroids during the first three postoperative days.

The *highest* daily excretion of total 17-hydrocycorticosteroids in the urine was recorded for case no. 1 on the third and fourth postoperative days, during which 173.5 mg and 179.2 mg in 24 hrs were excreted. This excretion is appreciably higher than any maximum reported previously. In the second patient (no. 2) with the highest excretion of total 17-hydroxycorticosteroids, the maximum value, 77.4 mg in 24 hrs, was recorded on the second postoperative day. Values over 50 mg in 24 hrs were determined for three other patients (nos. 4, 5, and 7), over 25 mg in 24 hrs in 18 patients (12 men and 6 women) and over 15 mg in 24 hrs in 29 patients (16 men and 13 women).

The excretions of total 17-hydroxycorticosteroids in the urine was over 50 mg during the *first postoperative* day in two patients during the second day in 3 cases and during the third day in 2 cases. An excretion was over 35 mg in 7 cases during the first day, in 12 cases during the second and in 5 cases during the third day and an excretion of 25 mg in 10, 15 and 5 cases, respectively, during the first three postoperative days.

The mean daily excretion of total 17-hydroxycorticosteroids during the *first three postoperative days* was over 15 mg in 22 patients (13 men and 9 women). A mean daily excretion of total 17-hydroxycorticosteroids of less than 15 mg during the same period was recorded for 30 patients (9 men and 21 women). A corresponding mean daily excretion of total 17-hydroxycorticosteroids of less than 5 mg was found for 10 patients (4 men and 6 women).

Over 25 mg of total 17-hydroxycorticosteroids were excreted during the *fourth postoperative day* by only two patients, during the fifth day by only one patient, and during subsequent days by none (the samples taken on the sixth day numbered 29, and those on the seventh day 18). Over 10 mg of total 17-hydroxycorticosteroids were excreted during the fourth day by 11 patients (samples from 48 patients), during the *fifth* day 7 patients (samples from 37 patients) and during the *sixt* day by 5 patients (samples from 28 patients) and during the *seventh* day by one patient (samples from 18 patients).

a. THE TIME OF INCREASED EXCRETION

Increased daily excretion of total 17-hydroxycorticosteroids was observed in most of the old patients for three days following the operations. In nine patients the excretion of total 17-hydroxycorticosteroids continued high for four days after the operations. In other patients the time of increased excretion usually was 3 days or less. However, in 4 patients the time of increased excretion of total 17-hydroxycorticosteroids continued longer than 4 days. In one patient the time of excretion was 7 days (no. 2), in two patients (nos. 14 and 21) 6 days, and in one (no. 8) 5 days.

In some of the cases the excretion of total 17-hydroxycorticosteroids evidently underwent no pronounced increase owing to decreased metabolism, impaired adrenal hormone secretion, or disturbed renal function. In one patient (no. 52) in whom no reaction was noted, the non-protein nitrogen was 84 mg per cent. It has been found previously that a decreased excretion of total 17-hydroxycorticosteroids follows impaired renal function resulting from testosterone administration (34). The cases included also patients with *shock*, of whom one (no. 16) had suffered a trauma and the other (no. 17) had a cardiac cancer. The former was 53 years old, the latter 55. The excretion of total 17-hydroxycorticosteroids in the former was low at first, but increased to 46 mg on the third day before death although the urine volume was small. This excretion of 17-hydroxycorticosteroids must be considered high. In the latter patient, the excretion was high on the first two postoperative days, but fell to nil on the third and fourth days. It may be concluded that a deficiency of adrenal function prevailed during the third and fourth days when administration of adrenocortical steroids would have been indicated.

The patients in whom the excretion of total 17-hydroxycorticosteroids increased only slightly included a large number of patients subjected to minor operations such as nailing of the femoral neck, prostate dilatation, gastrojejunostomy, various, biliary operations and explorative laparotomies. Radical operations involving stomach or lung, on the other hand, almost invariably lead to high excretions of total 17-hydroxycorticosteroids.

V DISCUSSION

Our results show that the excretion of total 17-hydroxycorticosteroids is more pronounced during the first two days after the operation in men than in women. In men the excretion has been about five times, and in women about three times as high as the excretion before operation. These values confirm fully those we have reported earlier (15). These steroids were excreted in the urine in amounts which were as high on the average as in the so-called depot-ACTH test in which ACTH is given intramuscularly in 40 mg doses twice daily and the excretion of total 17-hydroxycorticosteroids during this day is determined. According to Jenkins et al. (26), the mean value of the excretion after the depot-ACTH test during the first day is 15 mg.

The time of the increased excretion of total 17-hydroxycorticosteroids after operation is usually limited to three days. The third and fourth days are significant from the point of view of the recovery of the patient. The stress and the adaptation to the the conditions resulting from the operation generally last for a period of three days. In a few of the patients the reaction persisted from 4 to 6 days, and in one patient the whole period of observation, 7 days. The stress has evidently continued longer in the latter, but in most of the patients the excretion normalized already during three days after operation. One may enquire why the excretion becomes normal after the third postoperative day. It is obvious that the stress due to the operation has then already diminished also in the old age groups. It may also be assumed that the secretion of steroids by the suprarenal cortex may decrease owing to the increased 17-hydroxycorticosteroid content in the circulation which inhibit the secretion of adrenocorticotrophic hormones from the pituitary gland. There is a balance between the adrenocortical hormones from the adrenal glands and the ACTH from the anterior pituitary. The pituitary gland regulates the secretion of 17-

hydroxycorticosteroids according to the requirement of the cells in peripheral tissues during the increased stress. The 17-hydroxycorticosteroids content of the blood may inhibit the secretion of adrenocorticotrophic hormone by the pituitary gland (43). This factor may also fairly rapidly reduce the secretion of total 17-hydroxycorticosteroids from the adrenal glands from the fourth day after operation.

An increased excretion of total 17-hydroxycorticosteroids promotes the adaptation of the organism and its recovery from the stress caused by the operation. It restores the normal balance within the organism during and after the increased stress due to operation. An increased secretion of adrenal corticosteroids due to operation stress is a protective measure of the organism by which a normal balance is reached in the metabolism and blood circulation in conditions of increased stress due to operation.

In general, there is a correlation between the severity and nature of operation and the excretion of total 17-hydroxycorticosteroids. The mean maximum excretion of total 17-hydroxycorticosteroids, 33.9 mg in 24 hrs, was recorded for the group of thoracic operations. This was followed by the group of abdominal operations with 20.0 mg in 24 hrs, the group of urological operations with 16.8 mg in 24 hrs, and the group of femoral neck nailings with only 8.2 mg in 24 hrs. The excretion does not always seem to increase with the magnitude of the operation. In some of the patients an abundant excretion may follow also relatively minor operation.

In earlier studies relating to thoracic and abdominal operations (15), it was found that the increased excretion of total 17-hydroxycorticosteroids during the first three days following operations was higher in men (23.0, 28.6 and 14.8 mg in 24 hrs) than in women (16.3, 15.1 and 11.3 mg in 24 hrs) respectively. In this study we have now confirmed that the excretion after surgical operation is stronger also in old men (20.2 mg, 29.3 mg and 21.3 mg in 24 hrs during the first three days) than in old women (12.9 mg, 15.8 mg and 11.5 mg in 24 hrs). This may of course depend upon the different nature of the operations. The operations involving women included many femoral neck nailings which had only a relatively slight effect on the excretion of total 17-hydroxycorticosteroids. But it was also established that the excretion in the old men was stronger than in the old women in

the same operation group. For example, in the group of laparotomies, as well as in the more uniform group of gastric operations, this was found to be true. These findings lead one to conclude that, similarly as in younger individuals (15), the secretion of total 17-hydroxycorticosteroids by the adrenals is stronger in men than in women in the old age groups.

It is not very easy to evaluate the cause of the higher excretion of total 17-hydroxycorticosteroids in men than women in the older age group. However, the same relation between the excretions of total 17-hydroxycorticosteroids in men and women has been observed already in the younger age group and in the group of pulmonary operations (15). It is possible that the higher excretion in men than in women may be due to differences in the metabolism of the adrenocortical hormones in the two sexes. It may also be assumed that women adapt themselves to operations better than men and hence the stress caused by the operation is weaker in the former. Many surgeons have expressed the opinion that women endure operations better than men. This applies in particular also in the older age groups. We know that in women the hormone balance and pregnancies have during the ages improved the ability of the organism to withstand stress. For example, in connection with caesarean sections the excretion of total 17-hydroxycorticosteroids undergoes only a very slight increase (35), which is partly due to the improved hormone balance during pregnancy, but also to the fact that caesarean sections are relatively minor operations and recovery from them is generally good. Observations made in animal experiments have shown that female animals endure, for instance, hemorrhages, better than male when conditions are similar (14). Estrogenic hormones are able to protect the organism from vascular necrosis, while androgenic hormones may increase the possibility of vascular necrosis (29). It should be remembered, however, that in older age group the effect of estrogenic agents weakens with increasing age. At the same time the effect of androgens also diminishes. Men excrete larger amounts of androgenic hormones, 17-ketosteroids, in the urine than women in the younger age groups owing to the function of testes. It may be that the adrenals of men are able to produce larger quantities of corticosteroids than those of women.

The mean age of all the patients in our study, 63.5 years, is not very high. Certain conclusions may be drawn from the excretion of total 17-hydroxycorticosteroids when the patients are divided into two groups according to whether they were above or below the mean age. In both groups of old persons an increased excretion by both men and women was established, but this was weaker in the older age group than in the younger age group. It would be very interesting to determine the excretion of 17-hydroxycorticosteroids after operation also in very old persons, over 80 years of age. The function of the sympathetic part of the vegetative nervous system and the suprarenal medulla continues in old persons. These old persons have as large a content of adrenaline in their adrenals as younger persons (24), and in the former the excretion of adrenaline and noradrenaline in the urine is almost as large as in younger person (28).

It was observed in the present study that even old patients may react sensitively to operations as judged by their excretion of total 17-hydroxycorticosteroids. A comparison of our findings with previous ones relating to younger patients (15) reveals that the steroid secretion often increases clearly even in older patients after operations. The mean figures for the total 17-hydroxycorticosteroid excretion of women are almost equal in the abdominal and thoracic operation groups. When we divided our old patients into two age groups, we noted a slightly decreased mean excretion in the older group, but nevertheless the reactivity of the suprarenals had still remained fairly high in many cases. This is partly due to the diminished excretion of urine in the older age group on the first day after operation. Some of the patients of the older age group even exhibited a rather high excretion of total 17-hydroxycorticosteroids, which indicates a satisfactory activity of the adrenal cortex in these patients.

It is also apparent that the increase in the excretion is to some extent determined by the nature of the operation. Following major operations, such as those involving the lungs and stomach, the excretion has almost regularly increased, but after minor operations, such as nailings of the femoral neck, the increase has been relatively insignificant. It should be remembered that also many other factors, such as the general condition of the patient, may determine the degree of stress following an operation. The stress due to an

operation may vary in different persons. It is easily understood that the excretion will increase greatly after certain operations such, as pneumonectomies since the entire pulmonary circulation and with it the general circulation will have to adapt itself to new conditions. In addition, anoxia may develop in such patients, being either manifest or latent during several days following an operation. During operations involving the stomach the local conditions in the vicinity of the suprarenals and the local trauma resulting from the surgery may stimulate the secretion of corticosteroids by the suprarenals. Large operations may cause local traumas and pain associated with them, which may also increase the excretion of total 17-hydroxycorticosteroids. From animal experiments we know that certain factors such as low blood sugar content and oxygen deficiency may augment the activity of the adrenals. These same factors may also influence the excretion of total 17-hydroxycorticosteroids after an operation in old persons.

It is obvious that many of the stimuli that pass from the hypothalamus by the humoral route to the pituitary gland may influence the activity of the suprarenal cortex and thus increase the secretion of 17-hydroxycorticosteroids into the urine. Certain stimuli may also be of psychic origin.

The ability of man to secrete 17-hydroxycorticosteroids lasts longer than the ability to secrete other steroids. Sex hormones are produced mainly during the period of sexual maturity and their secretion is clearly weaker in children and in aged persons. Also the formation of hormones, including the pituitary hormones, may be assumed to be weaker in old persons. Consequently also the liberation of adrenal corticosteroids may be diminished. The socalled glucocorticoid system of the adrenals regulates the metabolic processes not only by increasing the glycogen reserve and protecting the cells, but also it promotes protein catabolism.

The secretion of androgenic substances, 17-ketosteroids, is weak in old persons (6,41). The excretion of androgenic hormones, 17-ketosteroids, does not increase as much as the excretion of 17-hydroxycorticosteroids under surgical stress in, for instance, pulmonary or abdominal operations (15). Therefore the excretion of total 17-hydroxycorticosteroids is a better measure of hormonal excretion in surgical stress than the excretion of 17-ketosteroids (15). If the

secretion of 17-hydroxycorticosteroids nevertheless continues, the equilibrium between anabolism and catabolism may be disturbed so that the catabolic process outweight the anabolic processes in the older age groups. The excretion of 17-ketosteroids does not increase as clearly in old as in young persons since the basal excretion is already lower in the former. This is a typical example of the effect of stress on the metabolism in old persons; the stress increases the amounts of glucocorticoids in the organism and this promotes the decomposition of proteins and the excretion of nitrogen. Owing to the deficiency in androgens, the protein synthesis remains inadequate.

We conclude that even in the old age groups the pituitary-adrenal system is often able to react normally during operations; in many cases so effectively that a normal reserve of adrenal corticosteroids and a normal excretion of pituitary adrenocorticotrophic hormone are maintained as in younger age groups (15). When we remember that ACTH increases the excretion of 17-hydroxycorticosteroids also in children, and already the stress of the delivery and the adaptation of infants during the first days of life cause an increased excretion of total 17-hydroxycorticosteroids (40), we note that the pituitary-adrenal system functions from childhood to old age to assist the organism in adaptation to stresses. It can, however, be suspected that the increase is not so high in old as in younger persons. On the other hand, an operation may impose a greater stress on an older than on a younger person and as a result the excretion of 17-hydroxycorticosteroids in the urine following the operation may be relatively greater in the older person when the stress is the same. Old persons may not be able to adapt themselves as well as young persons to the stresses of operations and consequently produce relatively large amounts of 17-hydroxycorticosteroids to fulfill the increased requirements of cells in the metabolism.

A prolonged administration of cortisone or of the adrenocorticotrophic hormone into the organism may inhibit the production of the adrenal corticosteroid hormone. The sudden discontinuation of the prolonged treatment with adrenocorticotrophic hormone or with cortisone may then lead to shock in stress, f.i. after operation. In such cases the treatment must be continued by giving adrenocortical hormones postoperatively, because the adrenals

otherwise cannot fulfill the increased requirements of adrenocortical hormones by the cells due to increased operative stress (11,1).

In some old persons it would be of advantage to determine the activity of the adrenals by means of the depot ACTH test already before major operations. The depot ACTH test can only reveal the activity of the suprarenal cortex, but not the ability of the pituitary gland to release adrenocorticotrophic hormone into the blood due to the increased stress of operations. On the basis of the ACTH test it is not possible to present any definite conclusions about the function of the pituitary gland.

By following a patient's general condition, it is sometimes difficult to predict the time he will require to recover from an operation. Only the extreme cases can be judged with any reliability. Extreme cases have been few in number in our series. One patient (no. 17) with shock may, however, be mentioned who exhibited a fairly high excretion during the first two postoperative days, but whose excretion then stopped almost completely. In this case the administration of adrenocortical hormones may be beneficial. A patient with a considerable weight loss and cachexia may also respond favourably to administration of corticosteroids before an operation. It should be remembered also that prophylaxis is often more effective than treatment for example, in the elimination of shock symptoms. Modern hydrocortisone preparations suitable for intravenous administration act more rapidly than earlier preparations which were given intramuscularly and hence they may be more effective in the treatment of shock conditions.

If the increase of the excretion of total 17-hydroxycorticosteroids is too small in the ACTH test the administration of ACTH or cortisone may improve the adaptation of the patient to the strain of operation and his general condition. The question arises whether administration of adrenal corticosteroids might have been appropriate in some of our cases and whether the indication can be confirmed on the basis of results obtained. In some cases the reaction was relatively weak after the operations but in these cases the operations were minor by nature. Clinical experience has shown that in certain cases of shock which have not responded to fluid therapy or other treatment, administration of hydrocortisone or a water-soluble ACTH preparation may yield favorable results.

One may ask whether a high excretion of 17-hydroxycorticosteroids in the urine after an operation has favorable effect on the recovery and general condition of the patient and on the postoperative course. We know that hydrocortisone produced by the adrenals, being a glucocorticoid, protects the organism against the ill effects of stress and at the same time mineralocorticoids are released which influence the mineral metabolism. In some cases the effect of hydrocortisone on the mineral metabolism may be a favourable one. Sodium chloride retention may promote the maintenance of adequate blood volume and pressure, but in some cases the changes in the mineral metabolism may be so pronounced that it may result e.g., in, mild oedema and retention of sodium chloride and water in the organism. The part played by aldosterone secreted by the adrenal cortex in regulating the mineral equilibrium during operations is yet unknown. Administration of pure glucocorticoids can, be expected to have a protective action on the circulation and metabolism in operative stress. Clinical experience has shown that fairly large amounts, 200-300 mg, of cortisone are often required during two or three days before and after operations to protect patients who have been subjected to large operations such as adrenalectomy or hypophysectomy. In such cases cortisone has promoted the adaptability of the patient to the stress caused by the operation and his later recovery (46, 49). Since hormones are required in so large amounts to protect the patient for 2-3 days before and after adrenalectomy or hypophysectomy, it is easy to understand how the relatively small amounts of 17-hydroxycorticosteroids secreted by the organism after operations can have favorable effect. It is more likely that these hormones promote the adaptation and recovery of the organism after the operation.

When assessing the excretion of total 17-hydroxycorticosteroids in the urine after operations, it is necessary to take into account the metabolic factors. A part of the 17-hydroxycorticosteroids are decomposed by metabolic processes and the part that becomes conjugated is secreted into the urine in this form. The conjugation takes place primarily in the liver and kidneys, and hence the function of the latter influences the excretion of 17-hydroxycorticosteroids in the urine. In old persons this excretion is also influenced by the urine volume. A diminished excretion of urine

is frequently observed in elderly patients during the first day following an operation. If the urine volume is very small, it may also lead to diminished excretion of steroids, as in some of our patients. It is generally believed that approximately 30 per cent of the steroids produced within the organism are excreted in the urine. Our studies confirm the opinion that the excretion of conjugated 17-hydroxycorticosteroids increases more after operations than the excretion of unconjugated or free 11-oxycorticosteroids (15). The organism tends to conjugate the 17-hydroxycorticosteroids, which are then eliminated in the urine. A limitation imposed in the present study was that it was necessary to disregard those patients by whom it was not possible to collect the urine excreted as they were not able to follow given instructions owing to being less indisposed after the operations and they had incontinentia on the first day postoperatively. Very frequently these patients were also the ones who had complications after the operations. For this reason, our series of old patients includes a few patients with postoperative complications, involving, for example, the heart and lungs, other than stress caused by the operation. In one of these cases a high value of the non-protein nitrogen in blood, over 80 mg per cent, was recorded. In this patient the excretion of steroids had not increased despite the fairly large operation he was subjected to. It should be remembered that the excretion of steroids is dependent also upon the function of kidneys (34). It is interesting to note that after the removal of one kidney (patient no. 6) the one remaining is able to secrete relatively large amount of 17-hydroxycorticosteroids. Only one kidney may thus be able to maintain a production of total 17-hydroxycorticosteroids that is higher than the normal.

VI. SUMMARY

The material included 52 elderly patients. Twenty two patients were men, 30 women. Their mean age was 63.5 years. The operations included 12 thoracic, 26 abdominal, 7 urological operations, and 6 nailings of femoral necks.

The total 17-hydroxycorticosteroid excretion was followed 1-3 days before and 1-7 days after the operation. In the *whole series* the mean excretion in the old age groups before the operation was 5.7 mg. During the first day after operation it was 16.0 mg, during the second 21.7 mg, and during the third 15.7 mg. From the fourth to seventh day the excretion gradually diminished to the level of basal excretion before the operation. The excretion during the second day after operation was nearly four times the mean excretion before the operation.

The mean excretion of total 17-hydroxycorticosteroids in the old age group during the first two postoperative days was higher in men than in women. The mean excretion for the *men* on the first day following operation was 20.2 mg, on the second day 29.3 mg and on the third day 21.3 mg, and for the *women* 12.9 mg on the first day, 15.8 mg on the second day, and 11.5 mg on the third day after operation. The excretion in men on the second postoperative day was twice as high as in the women. The same relationship was observed in the group of abdominal operations and also in the subgroup of gastric operations.

When the patients were divided into two age groups, the exretion on the second day was found to be higher in the younger than in older age group. This is partly due to the diminished urine volume in the latter and to the different nature of the operations in the two groups.

The mean excretion of total 17-hydroxycorticosteroids increased clearly during the first three days after the thoracic, abdominal and urological operations. Only a slightly increased excretion was observed after cholecystectomies and femoral neck nailings. The mean excretion of total 17-hydroxycorticosteroids on the second day was 33.9 mg in 24 hrs in the group of thoracic operations, 20.0 mg in 24 hrs in the group of abdominal operations, 16.8 mg in 24 hrs in the group of urological operations, and only 8.2 mg in 24 hours in the group of femoral neck nailings. The similar results were also observed on the first and third postoperative days.

VII. REFERENCES

1. Armstrong, T., and Jimenez, R. P.: Arch. med. de Cuba. Havana 1952:*3*:168.
2. Birke, G., Franksson, C., and Plantin, L-O.: Acta Endocrinol. 1955:*18*:201.
3. Bürger, M.: Ciba Symposium 1954:*1*:170.
4. Cole, W. H., Grove, W. J., and Montgomery, M. M.: Ann. Surg. 1953:*137*:718.
5. Dahl-Iversen, E.: Bull. Soc. Intern. Chir. 1955:XIV:53.
6. Dorfman, R. I., and Shipley, R. A.: Androgens, Biochemistry, Physiology and Clinical Significance 1956:397. John Wiley and Sons Inc. New York.
7. Engle, E. T.: Rec. Progr. Horm. Res. 1955:*VI*:291. Acad. Press, New York.
8. Engle, E. T., and Pincus, G.: Hormones and the Aging Process. 1956. Acad. Press, New York.
9. Franksson, C., and Gemzell, C. A.: Acta Chir. Scandinav. 1953: *106*:24.
10. Franksson, C., v. Euler, U. S., and Gemzell, C. A.: J. Clin. Endocrinol. & Metab. 1954:*14*:608.
11. Frazer, C. G., Preuss, F. S., and Bigford, W. D.: J.A.M.A. 1952: *149*:1542.
12. Galante, M., Rukes, M., Forsham, P. H., and Glenn, H.: Surg. Clin. North Am. 1954:*34*:1201.
13. Gold, N. I., Macfarlane, D. A., and Moore, F. D. J.: J. Clin. Endocrinol. & Metab. 1956:*16*:282.
14. Goldstein, M. S., and Harwood, T. C.: XX Congr. Intern. de Physiol. 1956:352. Bruxelles.
15. Halme, A., Pekkarinen, A., and Turunen, M.: Acta Endocrinol. 1957:*24*, suppl. *32*.
16. Hamburger, C., and Kaae, S.: Acta Endocrinol. 1949:*2*:257.
17. Hamilton, H. B., and Hamilton, J. B.: J. Clin. Endocrinol. 1948: *8*:433.
18. Hardy, J. D., Richardson, E. M., and Dohan, F. C.: Surg. Gyn. Obst. 1953:*96*:448.
19. Hasner, E., Carlsen, K., Engdahl, I., Klaerke, N., Paaby, H., Schultze, B., Sprechler, M., Sørensen, B., and Tobiassen, I.: Adrenals in Surgery, Munksgaard, Copenhagen 1952.
20. Hayes, M. A.: Surgery 1952:*32*:811.
21. Hayes, M. A.: Surgery 1954:*35*:174.
22. Howard, J. M., Olney, J. M., Frawley, J. P., Peterson, R. E., Smith, L. H., Davis, J. H., Guerra, S., and Dibrell, W. H.: Ann. Surg. 1955:*141*:314.
23. Hügin, W.: Praxis 1947:*16*:1454.
24. Ingier, A., and Schmorl, G.: Deutsch. Arch. klin. Med. 1911:*104*:125.

25. Iselstöger, H.: Subsidia Medica 1952:*4*:195.
26. Jenkins, D., Forsham, P. H., Laidlaw, J. C., Reddy, W., and Thorn, G. W.: Am. J. Med. 1955:*18*:1.
27. Kinnunen, O., Pekkarinen, A., and Simola, P. E.: Duodecim 1952:suppl. *25*.
28. Kärki, N.: Acta Physiol. Scand. 1956:*39*:suppl.132.
29. Lehr, D., and Martin, C. R.: XX Congr. Intern. de Physiol. 1956:555. Bruxelles.
30. Long, C. N. H.: Rec. Progr. Horm. Res. 1947:*I*:99. Acad. Press, New York.
31. Nylander, P. E. A., Pekkarinen, A., Aro, L., and Turunen, M.: Ann. Chir. et Gynaec. Fenn. 1953:*42*:7.
32. Paaby, H.: Acta Endocrinol. 1956:*21*:337.
33. Parsons, W. H., Whitaker, H. T., and Hinton, J. K.: Ann. Surg. 1956:*143*:845.
34. Pekkarinen, A., and Kasanen, A.: To be published.
35. Pekkarinen, A., and Rauramo, L., To be published.
36. Pekkarinen, A., and Turunen, M.: Acta Tub. Scandinav. 1955: *31*:241.
37. Peterson, R. E., and Wyngaarden, J. B.: Ann. New York Acad. Sc. 1955:*61*:297.
38. Roche, M., Thorn, G. W., and Hills, A. G.: New England J. Med. 1950:*242*:307.
39. Rukes, J. M., Orr, R. H., and Forsham, P. H.: Metabolism 1954: *3*:481.
40. Salmi, T., Heikkilä, S., and Pekkarinen, A.: Ann. Pediatr. Fenniae 1957:71.
41. Samuels, L. T.: Hormones and Aging Process 1956. Acad. Press, New York.
42. Sandberg, A. A., Nelson, D. H., Glenn, E. M., Tyler, F. H., and Samuels, L. T.: J. Clin. Endocrinol. & Metab. 1953:*13*:1445.
43. Sayers, G.: Physiol. Rev. 1950:*30*:241.
44. Sayers, G., and Sayers, M. A.: Rec. Progr. Horm. Res. 1948:*II*:81. Acad. Press, New York.
45. Selye, H.: J. Clin. Endocrinol. 1946:*6*:117.
46. Sprague, R. G., Randall, R. V., Salassa, R. M., Scholtz, D. A., Priestley, J. T., Walthers, W., and Bulbulian, A. H.: Arch. Int. Med. 1956:*98*:389.
47. Staland, B.: Nord. Med. 1954:*51*:415.
48. Thorn, G. W., Jenkins, D., Laidlaw, J. C., Goetz F. C., and Reddy, W.: Trans. Am. Phys. 1953:*66*:48.
49. Troen, P., and Rynearson, E. H.: J. Clin. Endocrinol. & Metab. 1956:*16*:747.
50. Turunen, M., and Tala, P.: Ann. Chir. et Gynaec. Fenn. 1952:*41*: 259.
51. Tyler, F. H., Schmidt, C. N., Eik-Nes, K., Brown, H., and Samuels, L. T.: J. Clin. Invest. 1954:*33*:1517.
52. Uotila, U., and Pekkarinen, A.: Acta Endocrinol. 1951:*6*:23.
53. Vihkari, S. J., and Thomasson, B. H., Acta Endocrinol 1957:*24*:361.